The INSURE study (INSIGHT MM, UVEA-IXA, REMIX): A pooled analysis of relapsed/refractory multiple myeloma (RRMM) patients treated with ixazomib-lenalidomide-dexamethasone (IRd) in routine clinical practice

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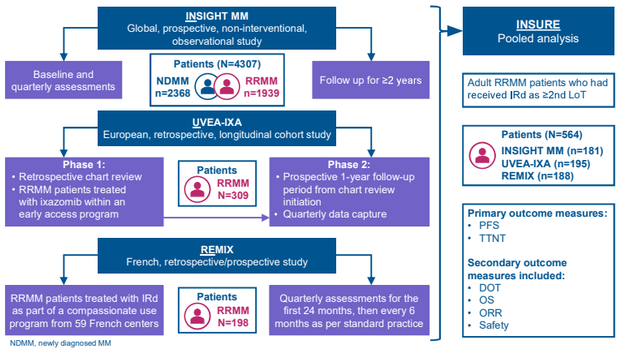
Background

- Ixazomib in combination with lenalidomide and dexamethasone, or IRd, has been approved for the treatment of RRMM based on the results of the TOURMALINE-MM1 phase 3 study:[1]
  - IRd demonstrated superior progression-free survival (PFS; median 20.6 vs 14.7 months; hazard ratio 0.74) and improved response rates (overall response rate [ORR] 78 vs 72%; ≥ very good partial response [VGPR] rate 48 vs 39%) versus placebo-Rd, with limited added toxicity[2]
- However, outcomes in routine clinical practice often differ from data reported in clinical trials for multiple myeloma (MM) therapies, being poorer for real-world versus clinical trial patients[3]
  - This discrepancy could be due in part to the fact that up to 72% of real-world patients with RRMM would not meet the eligibility criteria for randomized clinical trials[4]
  - Real-world studies with less stringent eligibility criteria may permit inclusion of a more diverse patient population and better inform on the effectiveness of therapies as used in routine clinical practice
- Several retrospective and prospective observational studies have now shown comparable effectiveness of IRd in ≥2nd line of therapy (LoT) in the real-world setting to the efficacy observed in TOURMALINE-MM1, with median PFS ranging from 11 to 43 months[5–11]
- The objective of the current analysis of a large, global dataset pooled from three observational studies is to investigate the effectiveness of IRd in the overall RRMM population, by LoT, and in subpopulations of patients defined by frailty status

Methods

- **Figure 2** summarizes the design of each observational study included in the INSURE pooled analysis:
  - INSIGHT MM is a large, prospective study which has enrolled 4307 MM patients from 15 countries in Europe, Asia, the US, and Latin America, with a planned follow-up of ≥2 years[12]
  - UVEA-IXA is a multicenter, longitudinal, retrospective cohort study of 309 RRMM patients receiving ixazomib-based treatment via an early access program in 8 countries in Europe[13]
  - REMIX is a retrospective/prospective study of 198 RRMM patients receiving IRd via a compassionate use program in France[11]
- The **INSURE** pooled analysis included adult patients with ≥2 prior MM therapy lines, and who had received IRd as ≥2nd LoT (**Figure 2**)
  - Time-to-event endpoints were analyzed in the overall analysis population, by LoT, and in subpopulations of patients defined by a simplified International Myeloma Working Group (IMWG)[14] frailty score (based on age, Charlson comorbidity index, and Eastern Cooperative Oncology Group performance status [ECOG PS]; 0–1 [non-frail] vs ≥2 [frail])[15] assessed at the start of IRd
    - Duration of treatment (DOT), time to next treatment (TTNT), PFS, and overall survival (OS) were analyzed using Kaplan-Meier methodology
  - Due to differences in how safety data were captured in each study, adverse events (AEs) and discontinuations/dose reductions due to AEs were reported separately for each study
  - Patients who were enrolled in >1 study were only counted once and only for the first LoT of IRd therapy received

Figure 2: INSURE pooled analysis: Summary of studies included



NDMM, newly diagnosed MM

Results

Patient demographics, disease characteristics, and treatment history

- In total, 564 patients enrolled in 17 countries were included in INSURE; most patients were enrolled in France (n=204, 36.2%) and the United Kingdom (n=144, 25.5%)
- Patients had received a median of 2 prior LoT (range: 1–12), with approximately 80% receiving IRd in either 2nd (40.8%) or 3rd (38.1%) LoT
- Patient baseline characteristics and disease characteristics at the start of IRd therapy overall and by line of IRd therapy are summarized in **Table 1**
  - Of the 406 patients with frailty scores recorded, 164 (40%) were defined as frail, with similar percentages (39–42%) of frail patients across all LoT

Question

Does IRd provide similar outcomes to TOURMALINE-MM1 for RRMM patients treated in routine clinical practice?

Study design

INSURE
Pooled, retrospective, global analysis

Data from 3 observational studies (N=564):
INSIGHT MM (n=181); UVEA-IXA (n=195); REMIX (n=188)

Primary outcomes: PFS and TTNT
Secondary outcomes include:
DOT, OS, ORR, and safety

Current analysis:
by LoT and frailty status

Results

Figure 1A: Median TTNT was 18.4 months overall, and was numerically longer in patients receiving IRd in earlier vs later LoTs

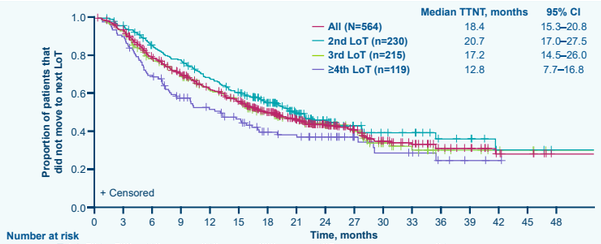
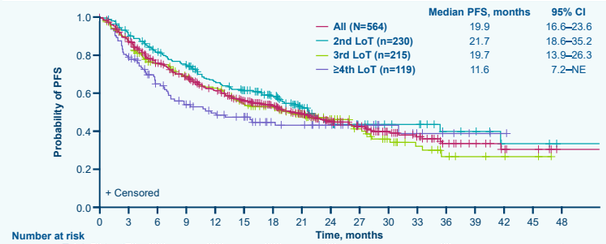


Figure 1B: Median PFS was 19.9 months overall, and was numerically longer in patients receiving IRd in earlier vs later LoTs



CI, confidence interval; NE, not estimable

Key take away

The effectiveness of IRd in routine clinical practice (median PFS 19.9 months, ORR 65%) is consistent with the efficacy of IRd observed in the registrational TOURMALINE-MM1 trial (median PFS 20.6 months, ORR 78%)[2] with no new safety concerns reported

Table 1: Patient baseline and disease characteristics, overall, by line of IRd therapy, and by frailty

Characteristic	All (N=564)	2nd LoT (n=230; 41%)	3rd LoT (n=215; 38%)	≥4th LoT (n=119; 21%)	Non-frail (n=242)	Frail (n=164)
Male, %	51.8	46.5	57.7	51.3	53.7	46.3
White/Caucasian race,* %	n=254 91.3	n=81 91.4	n=121 90.1	n=52 94.2	n=136 91.2	n=89 92.1
Age at start of IRd	n=553	n=227	n=210	n=116	n=242	n=164
Median, years (range)	68 (36–92)	69 (36–91)	68 (36–92)	68 (39–87)	67 (36–80)	76 (37–92)
Aged ≤65 years, %	36.7	36.1	37.1	37.1	47.1	17.1
Aged 66–75 years, %	42.0	37.4	43.3	48.3	50.8	29.3
Aged >75 years, %	21.3	26.4	19.5	14.7	2.1	53.7
M-protein type at diagnosis	n=384†	n=172	n=132	n=80†	n=169†	n=126
IgG / IgA / Light chain only†	54.7 / 19.0 / 21.1	59.9 / 20.3 / 17.4	48.5 / 19.7 / 23.5	53.8 / 15.0 / 25.3	55.0 / 16.6 / 22.0	51.6 / 20.6 / 23.8
Cytogenetic risk at diagnosis‡	n=242	n=118	n=82	n=42	n=116	n=71
High / standard	15.3 / 84.7	16.1 / 83.9	19.5 / 80.5	4.8 / 95.2	17.2 / 82.8	12.7 / 87.3
ECOG PS at the start of IRd,¶ %	n=492	n=196	n=194	n=102	n=242	n=164
0 / 1 / ≥2	32.3 / 50.2 / 17.5	32.7 / 50.5 / 16.8	33.0 / 51.5 / 15.5	30.4 / 47.1 / 22.5	47.1 / 52.9 / 0	7.3 / 47.6 / 45.1
Charlson comorbidity index at the start of IRd,¶ %	n=445	n=177	n=179	n=89	n=242	n=164
0 / 1 / ≥2	64.5 / 12.1 / 23.4	65.0 / 14.1 / 20.9	67.6 / 10.1 / 22.3	57.3 / 12.4 / 30.3	78.9 / 14.9 / 6.2	42.1 / 9.8 / 48.2
eGFR at the start of IRd,# %	n=520	n=211	n=199	n=110	n=235	n=156
≥60 / 30–60 / <30 mL/min	69.8 / 22.5 / 7.7	73.5 / 20.9 / 5.7	66.3 / 25.6 / 8.0	69.1 / 20.0 / 10.9	82.1 / 12.8 / 5.1	45.5 / 41.7 / 12.8
Biochemical progression only prior to IRd, %	n=488 56.4	n=200 55.0	n=190 61.6	n=98 49.0	n=213 67.6	n=143 47.6
Frailty score at the start of IRd, %	n=406	n=161	n=168	n=77	n=242	n=164
0–1	59.6	59.0	60.7	58.4	100.0	0
≥2	40.4	41.0	39.3	41.6	0	100.0

*Race not collected for REMIX study. †n=383 (overall), 79 (≥4th LoT) and 168 (non-frail) for light chain only assessment. ‡Defined as the presence of del[17p], t[4;14], t[14;16]; patients for whom an abnormality was not detected but were not assessed for all abnormalities were classified as missing. ¶From 1 year prior to until ≤ 90 days after the start of IRd therapy for INSIGHT MM and REMIX patients; date of assessment not available for UVEA-IXA patients. #As recorded for UVEA-IXA; for INSIGHT MM and REMIX, the values were estimated according to serum creatinine, age, and race. eGFR, estimated glomerular filtration rate; Ig, immunoglobulin

- Median time from MM diagnosis to start of IRd therapy was 39.3 months overall, and 29.7, 43.4, and 71.1 months for patients who received IRd as 2nd, 3rd, and ≥4th LoT, respectively
- Overall (n=562; data missing for 2 patients), the percentages of patients exposed or refractory (progressed on treatment or within 60 days of discontinuing treatment, or treatment-free interval between discontinuation and next index regimen of ≤60 days) to proteasome inhibitors (PIs) or immunomodulatory drugs (IMiDs) in any prior line were: PIs (bortezomib, carfilzomib, or ixazomib), 93%; lenalidomide, 30%; IMiDs (lenalidomide or pomalidomide), 31%
  - In 2nd / 3rd / ≥4th LoT, 93 / 93 / 95%, 13 / 28 / 68%, and 14 / 29 / 70% of patients were exposed or refractory in any prior line to a PI, to lenalidomide, or to an IMiD, respectively

Outcomes

- Median duration of follow-up from start of IRd for all patients was 18.5 months
- Median DOT was 14.0 months overall, and was numerically longer in patients receiving IRd as 2nd or 3rd (16.9 and 14.8 months) vs ≥4th LoT (7.5 months) and in non-frail (16.1 months) vs frail (9.7 months) patients (**Figure 3**)
- Median TTNT was 18.4 months overall, and was numerically longer in patients receiving IRd in earlier vs later LoTs (**Figure 1A**, **Summary Panel**) and in non-frail vs frail patients (**Figure 4A**)
- 280 patients (49.6%) had progressed or died; median PFS was 19.9 months overall, and numerically longer in patients receiving IRd in earlier vs later LoTs (**Figure 1B**, **Summary Panel**) and in non-frail vs frail patients (**Figure 4B**)
- 184 patients (32.6%) had died. OS data were not mature, with median OS not reached overall or in patients receiving IRd as 2nd or ≥4th LoT (3rd LoT, 34.9 months; 95% CI: 27.2–NE). In non-frail vs frail patients median OS was not reached vs 20.1 months (95% CI: 17.5–30.4)

Figure 3: Figure 3. Kaplan–Meier analysis of DOT with IRd (A) overall and by LoT and (B) by frailty

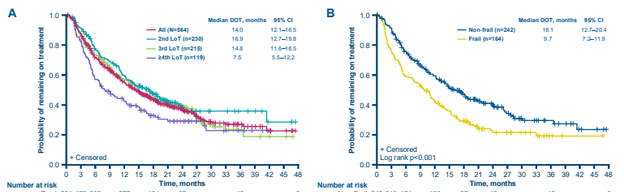
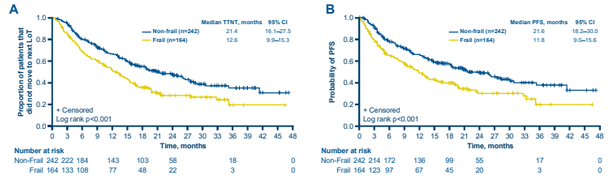
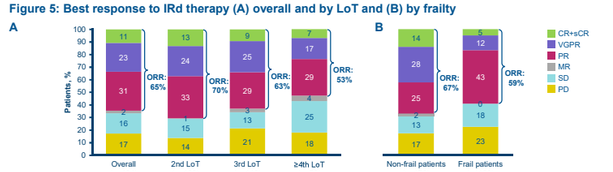


Figure 4: Kaplan–Meier analysis of (A) TTNT and (B) PFS with IRd by frailty



- Best response to IRd therapy among the 404 response-evaluable patients is shown overall, by LoT and by frailty status in **Figure 5**
  - ORR was 70%, 63%, and 53% among patients receiving IRd as 2nd, 3rd, and ≥4th LoT, with a median time to best response of 3.9, 5.2, and 3.5 months, respectively
  - There was a higher proportion of non-frail (42%) vs frail (17%) patients with ≥VGPR

Figure 5: Best response to IRd therapy (A) overall and by LoT and (B) by frailty



Median time to best response, months (range)	4.0 (0–47.7)	3.9 (0.2–47.7)	5.2 (0–32.7)	3.5 (0–28.7)	4.7 (0.5–25.0)	3.2 (0–32.7)

Response data missing for 160 patients overall: 47, 66, and 47 for patients receiving IRd as 2nd, 3rd, ≥4th LoT, respectively; 69 non-frail and 44 frail patients. Percentages may not sum due to rounding. ORR = PR + VGPR + CR + sCR. CR, complete response; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent CR; SD, stable disease

Safety

- Dose reductions and discontinuations and the most common AEs leading to ixazomib dose reduction and discontinuation in INSIGHT MM and UVEA-IXA are shown in **Table 2**
- Rates of AEs and serious AEs and most common AEs reported in REMIX are shown in **Table 3**

Table 2: Dose reductions and discontinuations due to AEs in INSIGHT MM and UVEA-IXA

		INSIGHT MM (n=181)	UVEA-IXA (n=195)
Dose reductions, %	Ixazomib	13.8	9.2
	Lenalidomide	19.3	9.2
	Dexamethasone	11.6	1.0
Discontinuations, %	Ixazomib	29.8	16.9
	Lenalidomide	22.7	14.9
	Dexamethasone	18.2	9.7
Most common* AEs leading to ixazomib dose reduction, %		n=25	n=18
Diarrhea		20.0	38.9
Peripheral neuropathy		24.0	16.7
Thrombocytopenia		20.0	11.1
Fatigue		16.0	5.6
Nausea/vomiting		8.0†	16.7
Most common* AEs leading to ixazomib discontinuation, %		n=54	n=33
Thrombocytopenia		18.5	24.2
Diarrhea		9.3	18.2
Infections and infestations		14.8	6.1‡
Peripheral neuropathy		7.4	12.1
Fatigue		11.1	0

*Occurring in >10% of patients with dose reduction or discontinuation in at least one study. †Nausea only. ‡Infection only.

Table 3: REMIX safety summary

	REMIX (n=188)
AEs, %	64.9
Serious AEs, %	37.8
Most common* AEs, %	
Diarrhea	14.9
Thrombocytopenia	14.4
Most common* serious AEs, %	
Plasma cell myeloma	5.3
Thrombocytopenia	5.3

*Occurring in >10% of patients for AEs and >5% for serious AEs.

Conclusions

- These findings from INSURE, an analysis of a large, global, pooled dataset of 564 patients, show that the effectiveness of IRd in routine clinical practice (median PFS 19.9 months, ORR 65%,) is consistent with the efficacy of IRd observed in the registrational TOURMALINE-MM1 trial (median PFS 20.6 months, ORR 78%)[2] with no new safety concerns
- Our results suggest a greater benefit of treatment with IRd in earlier versus later lines, consistent with reports from previous, smaller real-world studies of IRd in RRMM patients[5,8,9]
- Assessment of TTNT (a real-world proxy for PFS) and PFS was feasible in INSURE with similar median values overall and similar trends by LoT; this supports the robustness of the observed effectiveness of IRd
- In addition, this analysis provides important insights on the effectiveness of IRd in frail patients, helping to increase the understanding of the achievable outcomes in this subpopulation; future analyses should focus on further evaluation of the effectiveness of therapies in frail and non-frail MM patients in the real world
- This study may be impacted by typical limitations inherent to real-world studies, including selection and confounding biases, missing data, and inconsistent data reporting across study sites

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Disclosures

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